IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Jackson, et al.		
Application No.: 10/828,395		
Filed: 4/19/2004	Group Art Unit:	1635
Title: Method for Treatment of Angiogenic Disorders	Examiner:	Tracy Ann Vivlemore
Attorney Docket No.: UBC.P-032		

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the rejection mailed 5/25/2006. This was the second rejection of the claims and therefore an Appeal is permitted. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is The University of British Columbia. The application is licensed to OncoGenex Technologies Inc.

Related Appeals and Interferences

Although the subject matter is different, some of the legal issues in this case are related to the decision in Appeal No. 2005-2447. A copy of this decision is attached in the Appendix. Applicants note that the written description rejection, to the extent it was affirmed in this decision is the subject of a further pending appeal to the Court of Appeals for the Federal Circuit.

Status of Claims

Claims 1-3, 6-8 and 11-13 are rejected and are the subject of this appeal. Claims 4, 5, 9, 10, 14 and 15 are withdrawn.

Status of Amendments

No amendment after final has been filed. All amendments filed have been entered.

Summary of Claimed Subject Matter

The present invention relates to the treatment of a non-cancerous angiogenesis-related diseases using a therapeutic composition that is effective to reduce the effective amount of clusterin in the individual (Independent Claim 1), or to the method of reducing angiogenesis (Independent Claim 6). The method of claim 1 is also specifically claimed for treatment of humans (Independent Claim 11).

Clusterin is a known protein with a known sequence (Page 4, lines 4-10), and oligonucleotide therapeutics for its inhibition are disclosed in the art (Page 5, lines 11-15) and in the application (Seq. ID Nos. 2-23). The present invention is based on the finding of the present inventors that reduction in clusterin results in a reduction of angiogenesis (Page 1, lines 14-15) and the recognition that this means that the multiplicity of non-cancerous diseases in which angiogenesis is a factor can therefore be treated by reduction of clusterin (Page 1, lines 6- 13 and Table 4).

Grounds of Rejection to be reviewed on Appeal

Claims 1, 6 and 11 are rejected under 35 USC § 112, first paragraph, for lack of written description.

Claims 1-3, 6-8 and 11-13 are rejected under 35 US § 112, first paragraph for lack of enablement.

Claims 1, 2, 6, 7, 11 and 12 are rejected under 35 USC § 102(b) as anticipated by Monia et al, US Patent No. 6,383,808.

Argument

A. Written Description Rejection

Claims 1, 6 and 11 are rejected under 35 USC § 112, first paragraph, for lack of written description. The Examiner states that

> the instant claims do not satisfy the written description requirement because the description of antisense oligonucleotides and siRNAs targeted to human clusterin provided in the specific does not describe the full genus of nucleic acid and non-nucleic acid inhibitors that are encompassed by the claims. The structure of an antisense oligonucleotide does not lead the skilled artisan to the structure of any other type of inhibitor that has the function of inhibiting clusterin in all species.

(Office Action of May 25, 2006, Page 2) From this explanation, it is apparent that the Examiner is not looking at the question of whether or not the specification conveys to the person skilled in the art that the Applicants had possession of (i.e had conceived of) the invention as claimed, but rather whether they have provided an exhaustive list of examples including those that have not yet been invented. This is not the proper legal standard, and the rejection should therefore be reversed.

The Court of Appeals for the Federal Circuit has observed that:

> the "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed.

Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). Further, the Federal Circuit has stated that the purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000). The Federal Circuit has never said, however, that the written description requirement is intended to limit an applicant to the specific examples set forth in the application when the contribution to the art is greater in scope than those specific examples.

In rejecting the claims for lack of compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). Here, the Examiner has not offered a reason **why** a person skilled in the art would not recognize in the description a disclosure of the full scope of the invention as claimed. Instead, the Examiner's position is essentially that the specification does not provide any description, structural or otherwise, of clusterin inhibitors other than the antisense oligonucleotides or siRNA inhibitors. Compliance with the written description requirement does not require that the compounds disclosed be "representative" of the full scope of the claim, nor does it require a certain number of examples. It only requires that the specification convey in some manner, that the inventor had possession of the invention as claimed.

In this case, claims 1 and 6 as originally filed were not limited to oligonucleotide therapeutics. Furthermore, antisense oligonucleotides are identified as preferred (¶ 009) Further, the application consistently refers to a "therapeutic agent" generically (¶¶ 016 and 021) and the possibility of using an antibody therapeutic to miodify clusterin to an inactive form is specifically mentioned (¶ 016). Thus, the specification clearly conveys the inventors' understanding that the invention was broader than just the use of olignucleotide therapeutics.

It is further noted that the focus of the rejection in this case is not on the **invention** as claimed, but rather on one aspect of the invention, namely the therapeutic agent. The test for compliance with the written description requirement, however, should properly look at the invention as claimed to see if it fairly reflects the inventors' contribution to the art. Indeed, the Federal Circuit has repeatedly referred to a consideration of the **invention**. *Moba B.V. v. Diamond Automation Inc.*, 325 F.3d 1306, 1320, 66 USPQ2d 1429, 1439 (Fed. Cir. 2003)("the test for compliance with §112 has always required sufficient information in the original disclosure to show that the inventor possessed **the invention** at the time of the original filing"; *Vas-Cath, Inc. v. Mahurkar*, 935 F. 2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.

1991)("the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of **the invention**. The invention is for purposes of the 'written description' inquiry, whatever is now claimed."); *Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000) ("The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] **invented what is claimed**'").

Consideration of *In re Fuetterer*, 319 F.2d 259, 138 USPQ 217 (CCPA 1963) also demonstrates the importance of focusing on the invention as claimed. The claims in Fuetterer referred to a rubber stock composition useful in producing tire treads and included a functional recitation of "an inorganic salt capable" of maintaining an homogeneous distribution of another component in the composition. The disclosure listed the function desired and four members of the class having that function. The CCPA found that this claim met the requirements of 35 U.S.C. § 112, first paragraph, stating that:

> Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.

319 F.2d at 265, 138 USPQ at 223.

In the present case, Applicants' invention is not the therapeutic agent *per se*. It is also not the identification of clusterin, nor any and all inhibitors of clusterin. Applicants' invention is a method for treating angiogenesis-related diseases and redusing angiogenesis v\by reducing the amount of clusterin. The Examiner is not looking at this invention nor at the teaching of the specification, however, but rather seems to require Applicants to identify and test compounds for

every conceivable therapeutic type for performing the methods of the invention in order to secure generic protection for their invention. In doing so, they are focusing on the description of the compositions used, as opposed to the description of the invention as a whole.

In the absence of extensive research conducted prior to filing of the application, the Examiner effectively requires that the claims must be limited to the specific examples, leaving Applicants at the mercy of every copyist who chooses to steal their invention by using some different active agent than those specifically disclosed. Applicants are aware of no such burden imposed by the law of the United States. Indeed, to paraphrase the portion of *Fuetterer* cited above, if others in the future discover therapeutic agents additional to those enumerated that have such properties [inhibiting clusterin], it is clear appellant will have no control over them *per se*, and equally clear their claims should not be so restricted that they can be avoided merely by using some therapeutic agent not named by Applicants in their disclosure.

Furthermore, the application of the written description requirement in this manner is contrary to the public policy underlying patent protection. In *Transco Prods. Inc. v. Performance Contracting, Inc.*, the Federal Circuit considered whether updating of best mode in continuation applications was required and observed that "such a rule would subvert the patent system's goal of promoting the useful arts by encouraging early disclosure. 38 F. 3d 551, 558, 32 USPQ 2d 1077, 1082 (Fed. Cir. 1994). The same is true of the application of the written description requirement made in this case. If an applicant that has discovered a therapeutic method is required to test representatives of multiple types of therapeutics in order to secure meaningful patent protection, disclosure of therapeutic methods will be delayed, if it occurs at all.

For these reasons, Applicants submit that the written description rejection of claims 1, 6 and 11 should be reversed.

B. Enablement Rejection

Claims 1-3, 6-8 and 11-13 are rejected under 35 US § 112, first paragraph for lack of enablement. The Examiner asserts that the specification is enabling only for reduction of

administration of an antisense oligonucleotide targeted to clusterin in cells in *vitro*. This rejection is very similar to the enablement rejection that was reversed in the related case referenced above.

The burden is on the Examiner to put forward reasoning inconsistent with enablement. *In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982). Furthermore,

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond to those used in describing and defining the subject matter sought to be patents *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112, *unless* there is a reason to doubt the objective truth of the statements contained therein, which must be relied upon for an enabling disclosure.

In re Marzocchi, 169 USPQ 367 (CCPA 1971). General teachings about variability and difficulties that are divorced from a disclosure of a specific target and specific operative species, and which the Examiner has not even attempted to relate to difficulties that might be **specific** to extending the disclosure to the allegedly non-enabled materials, are simply not enough to meet this burden.

The basis for the Examiner's rejection is a collection of review articles that address some of the problems that are encountered with antisense therapy as a general matter. None of the references are effective to cast doubt on the specific statement of the application in the specific context of clusterin.

The generalized difficulties that the Examiner identifies are with delivery, target accessibility and the potential for unpredictable non-specific effects. (Office Action of December 27, 2005, Page 7.) Applicants submit that target accessibility is not an issue since there is no reason to imagine that the accessibility is different between a living cell *in vitro* and the same living cell *in vivo*. Furthermore, the issue of potential and unpredictable side effects is an issue for the FDA and has nothing to do with enablement. Thus, the only expressed reason that passes even first muster is the assertion of generalized teachings of problems with delivery. These

assertions are just that, however, generalized, and do not meet the burden of saying why the person skilled in the art could not proceed without undue experimentation.

Notwithstanding the insufficiency of the response, Applicants submitted a copy of a declaration filed in a related case, Serial No. 09/967,726, in which clinical trials of an antisense targeted to clusterin are reported. A copy of this declaration is attached in the Appendix hereto. While these trials are preliminary and directed to toxicity assessment, it is apparent that no special carrier was required to achieve *in vivo* reduction of clusterin expression in cancer cells of varying types and locations whose common characteristic was the overexpression of clusterin. Since angiogenesis is also associated with increased clusterin expression, and since the present application shows that reduction of clusterin expression reduces angiogenesis, the teaching of the application is reasonably enabling and therefore sufficient.

Applicants further note that the Examiner has identified the experimentation that is alleged to be necessary on Page 10 of the Office Action mailed December 27, 2005. There she states that "a number of variables would need to be **optimized.**" (emphasis added) Enablement is not about optimization, however, and thus it appears that the Examiner is applying an improper standard. The Examiner then proceeds to identify three factors to be optimized namely (1) the mode of delivery, the amount of antisense, and steps to ensure sufficient duration for therapeutic benefit., and states that

> while optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention ... without undue trial and error experimentation.

This, however, is precisely what is done every time a drug is tested through clinical trials to determine how, how much and how often it will be administered. Enablement does not require that clinical trials be completed.

C. Anticipation Rejection

Claims 1, 2, 6, 7, 11 and 12 are rejected under 35 USC § 102(b) as anticipated by Monia et al, US Patent No. 6,383,808. The Examiner relies on Monia for a teaching of "a method of treating an animal having a disease associated with expression of clusterin using an antisense oligonucleotide" (refering to Col. 3, lines 40-46), and for a teaching that atherosclerosis as a disease that is "a non-cancerous angiogenesis related disease." (referring to Col. 2, line 65 - Col. 3, line 6). Based on these disclosures, the Examiner argues that the Monia reference discloses "a method of inhibiting clusterin expression in disease-associated cells and individuals suffering from such diseases that absent evidence to the contrary would reduce angiogenesis and treat a non-cancerous angiogenesis related disease." (Office Action of May 25, 2006, Page 4)

Anticipation requires a teaching in a reference of each and every aspect of the claimed invention. Furthermore, in order for a *prima facie* rejection to be presented, "it is incumbent upon the examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990), *citing Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

In the present case, independent claims 1 and 11 are methods for treatment of a non-cancerous angiogenesis related disease. The Examiner does not allege that Monia teaches treatment of a non-cancerous angiogenesis related disease. Rather, the Examiner only asserts that Monia discloses "a method of inhibiting clusterin expression in disease-associated cells and in individuals from such diseases." This is not merely a semantic distinction because the assertion of any therapeutic benefit in Monia is entirely speculative. For example, the passage cited by the examiner at Col. 3, lines 4-6 states only that "the pharmacological modulation of clusterin activity and/or expression may therefore be an appropriate point of therapeutic intervention in pathological conditions." Not only is this statement cast in terms of what "may" be useful, it uses the term "modulate" which would encompass both decreasing expression and enhancement of expression. It is noted that the Examiner also argues that Monia teaches "treatment of cells associated with a disease." This is not the same as what is claimed, however,

which requires treatment of the disease, and thus a therapeutic benefit relative to the disease. This is not alleged to be shown in Monia. Thus, the Examiner simply has not established that Monia teaches the invention of claim 1 or 11, and the rejection of these claims and the claims dependent thereon should be reversed.

With regard to claim 6, this claim refers to a method for reducing angiogenesis. The Examiner admits that the Monia reference "is silent with regard to inhibition of clusterin resulting in reduction of angiogenesis." (Office Action, Page 4) Thus, it would appear that the Examiner is either ignoring the reference to reduction on angiogenesis in the claim, or relying on some theory of inherency in support of this rejection. Neither is proper.

The words that the Examiner is failing to take into account are not located only in the preamble. Claim 6 reads:

> 6. **A method for reducing angiogenesis** in a non-cancerous angiogenesis-related disease, comprising the step of treating cells associated with the non-cancerous angiogenesis-related disease with amount of a therapeutic composition effective to reduce the effective amount of clusterin in the cells, and **thereby to reduce the occurrence of angiogenesis.**

(emphasis added) Nevertheless, case law on preamble language is instructive in determining the significance . The Court of Appeals for the Federal Circuit has recently observed that

> "In general, a preamble limits the [claimed] invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808, 62 USPQ2d 1781, 1784 (Fed. Cir. 2002) (quoting *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999)). "[A] claim preamble has the import that the claim as a whole suggests for it. In other words, when the claim drafter chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects." *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995).

Eaton Corp. v. Rockwell International Corp., 66 USPQ2d 1271 (Fed. Cir. 2003). In the present case, the ignored language cannot be deemed superfluous, since it says what is being accomplished by the method, namely a reduction in angiogenesis, and the claim without these words is meaningless. Indeed, the notion that preamble language is generally meaningless in method claims would render second use method claims impossible.

The importance of the preamble in method claims of this type is reflected in *Jansen v. Rexall Sundown, Inc,* 68 USPQ 2d 1154 (Fed. Cir. 2003). In that case, the claims at issue were directed to "a method of treating or preventing macrocytic-megaloblastic anemia" by administration of a composition of defined components "to a human in need thereof." The accused product was a dietary supplement having a composition as defined in the claims. It was lableled for uses that did not include treating or preventing macrocytic-megaloblastic anemia. The Federal Circuit found that the claims were limited to the use, as stated in the preamble. Similarly, in *Rapoport v. Dement*, 59 USPQ2d 1215 (Fed. Cir. 2001) a claims directed to "a method for treatment of sleep apneas" was interpreted as being just that, and not a method for treating symptoms associated with sleep apneas, which was found in the art.

In *Jansen* the Federal Circuit observed that

> in both *Rapoport* and this case, the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' In both cases, the claims' recitation of a patient or a human 'in need' gives life and meaning to the the preambles' statement of purpose. The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method is performed.

Jansen at 1158. In this case, claim 6 is directed to "a method for reducing angiogenesis in a non-cancerous angiogenesis-related disease." Treatment is given to "cells associated with a non-cancerous angiogenesis-related disease" and the result is an reduction in angiogenesis. These recitations are equivalent to the "in need" statements of *Jansen* and *Rapoport*. The acknowledged absence of disclosure of angiogenesis reduction in the cited reference is therefore fatal to an anticipation rejection, and the rejection should be reversed.

Furthermore, while the Examiner has identified atherosclerosis as a condition identified in the present application as being an angiogenesis related disease, it cannot be inferred from the reference that treatment of atherosclerosis using clusterin reduction would result in reduction in angiogenesis or that any therapeutic benefit that might flow from such a treatment would have anything to do with angiogenesis. Indeed, in the Background section of Monia, clusterin is identified as a circulating high density lipoprotein that is involved in cholesterol metabolism and that is a regulator of lipid transport and redistribution. (Col. 1, lines 42-62) Thus, Monia teaches a previously known activity in the context of atherosclerosis that has nothing to do with angiogenesis.

Thus, Applicants submit that the rejection of claim 6 and claims 7 and 8 dependent thereon as anticipated should be reversed.

Respectfully submitted,

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Claims Appendix

1. A method for treatment of a non-cancerous angiogenesis-related disease, comprising the step of administering to an individual suffering from the non-cancerous angiogenesis-related disease an amount of a therapeutic composition effective to reduce the effective amount of clusterin in the individual.

2. The method of claim 1, wherein the therapeutic composition comprises an antisense oligonucleotide complementary to the sequence of human clusterin (Seq. ID. No. 1).

3. The method of claim 2, wherein the antisense oligonucleotide is selected from the group consisting of oligonucleotides whose sequence consists essentially of a sequence as set forth in Seq. ID Nos. 2- 15.

6. A method for reducing angiogenesis in a non-cancerous angiogenesis-related disease, comprising the step of treating cells associated with the non-cancerous angiogenesis-related disease with amount of a therapeutic composition effective to reduce the effective amount of clusterin in the cells, and thereby to reduce the occurrence of angiogenesis.

7. The method of claim 6, wherein the therapeutic composition comprises an antisense oligonucleotide complementary to the sequence of human clusterin (Seq. ID. No. 1).

8. The method of claim 7, wherein the antisense oligonucleotide is selected from the group consisting of oligonucleotides whose sequence consists essentially of a sequence as set forth in Seq. ID Nos. 2- 15.

11. A method for treatment of a non-cancerous angiogenesis-related disease in a human individual suffering from the con-cancerous angiogenesis-related disease, comprising the step of administering to the individual an amount of a therapeutic composition effective to reduce the effective amount of clusterin in the individual.

12. The method of claim 11, wherein the therapeutic composition comprises an antisense oligonucleotide complementary to the sequence of human clusterin (Seq. ID. No. 1).

13. The method of claim 12, wherein the antisense oligonucleotide is selected from the group consisting of oligonucleotides whose sequence consists essentially of a sequence as set forth in Seq. ID Nos. 2- 15.

Evidence Appendix

Copy of Declaration from 09/967,726 entered with the amendment filed March 24, 2006.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Gleave, et al. Application No.: 09/967,726 Filed: 9/28/2001 Title: Chemo-and Radiation-sensitization of Cancer by Antisense TRPM-2 Oligodeoxynucleotides Attorney Docket No.: UBC.P-022 Customer No.: 021121	Group Art Unit: 1635 Examiner: Tracy Ann Vivlemore Confirmation No: 6881

Commissioner for Patents

PO Box 1450

Alexandria, VA 22313-1450

DECLARATION UNDER RULE 132

The undersigned each hereby declare as follows:

1. I am a named inventor of the above-captioned application. As such, I am familiar with the application, including the claims.

2. This declaration is submitted to set forth results from clinical trials that have been conducted since the filing of the application.

3. This declaration is signed by less than all of the inventors, because the other inventors, H. Miyake and T Zellweger, are no longer associated with the project, and have had no involvement, and thus no personal knowledge of the trials reported here.

4. Limited clinical testing (two Phase I studies) has been conducted to evaluate toxicity of OGX-011, an antisense oligonucleotide that has the sequence as set forth in Seq. ID NO.: 4 of the above-captioned application. The oligonucleotide is modified as described in Application Serial No. 10/080,794. A total of 25 patients with localized prostate cancer with high risk features were enrolled in the first study. In the second study, a total of 30 patients suffering from renal cancer, non-small cell lung cancer, ovarian cancer, peritoneal cancer or prostate cancer were enrolled, each of whom was refractory to one or more prior treatment regimens.

5. In both phase I studies, antisense treatments were made at levels of 40, 80, 160, 320, 480 or 640 mg and administered intravenously 3 times during the first week, and once a week thereafter. In the first phase I study, antisense therapy was combined with concurrent hormone ablation therapy for 5 weeks prior to radical prostatectomy. Concentrations of OGX-011 in prostate tissue and of TRPM-2 mRNA and protein in prostate and lymph node tissue were determined. At all levels of antisense, dose-dependent reduction in levels of TRPM-2 mRNA was observed in the lymph nodes of the patients treated, and in laser captured, micro-dissected prostate cancer levels, indicating that all of the amounts of antisense tested had a measurable affect at the expression level. The amount of TRPM-2 in serum also decreased in a dose-dependent manner.

6. This study established a dose of 640 mg as the recommended dose based on safety, tolerability, and tissue levels of antisense and TRPM-2 mRNA and/or protein.

7. In the second Phase I study, two schedules of concurrent docetaxel treatment were evaluated: 30 mg/m^2 weekly or 75 mg/m^2 every three weeks. Of 18 patients with measurable disease, the interim response rate (the study is still in progress) was 38.9%, including 33.3% with stable disease, and 5.6% achieving an objective partial response.

8. Two ovarian cancer patients showed reductions in the measured amount of the tumor marker CA125. In one patient receiving 160 mg OGX-011, the amount of CA125 marker decreased from 19,600 to 4720 over 71 days after commencement of treatment. In another who received 480 mg OGX-011, the marker level decreased from 2000 before treatment to around five hundred after 33-44 days. A slight increase to around 900 was observed during a second treatment cycle. Other patients with ovarian cancer had low initial CA125 and so a decrease could not be evaluated.

9. Two prostate cancer patients showed reduction in the amount of PSA tumor marker. In one patient receiving 40 mg OGX-011, the PSA level decreased from 90 prior to therapy to 35 after 4 treatment cycles at approximately 45 day intervals, and remained at 56 at a later date. In a second patient receiving 320 mg OGX-011, the PSA level dropped from a pre-treatment level of 1478 to a level of about 425 after 4 cycles of treatment.

10. The selection of initial dosages for this study was consistent with standard protocols for clinical trials to evaluate toxicity, and no experimentation was needed to arrive at dosage levels that produced observable reduction in TRPM-2 mRNA or serum TRPM-2.

11. While the data in this study is preliminary and difficult to draw many conclusions from because of the small sample size, the number of variables that were considered, including prior treatment of the patients, and the short duration of the test, several conclusions can be drawn. Standard

protocols for trial design were used and arrived, without experimentation, at working levels for antisense dosing that produced reduction in TRPM-2 mRNA and serum TRPM-2 without significant toxicity, and this treatment in combination with docetaxel produced beneficial results in patients who had been refractory to prior treatment.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

dated: April 6/05

Martin Gleave

dated: April 5/05

Paul Rennie

dated: April 5/05

Colleen Nelson

Related Proceedings Appendix

Decision from Appeal No. 2005-2447

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARTIN GLEAVE and HIDEAKI MIYAKE

Appeal No. 2005-2447
Application No. 09/619,908

HEARD: October 18, 2005

Before SCHEINER, ADAMS and MILLS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of claims 1-23 and 26-40. Claims 24 and 25, also pending in the application, have been allowed.

BACKGROUND

> Insulin-like growth factor (IGF)-I and IGF-II are potent mitogens for many normal and malignant cells. Accumulating evidence suggests that IGFs play an important role in the pathophysiology of prostatic disease and breast cancer. . . .
>
> The biological response to [IGFs] is regulated by various factors, including IGFBPs [(insulin-like growth factor binding proteins)]. To date, six IGFBPs have been identified whose function is believed to involve modulation of the biological actions of the IGFs through high affinity interactions . . . However, some evidence suggests biological activity for IGFBPs that are independent of IGFs, . . . and both stimulatory and inhibitory effects of IGFBPs on cell proliferation have been reported under various experimental conditions. . . .

Specification, pages 1-2.

"[P]rostate cancer is an androgen-sensitive tumor, [thus,] androgen withdrawal . . . is utilized in some therapeutic regimens . . . [and] leads to extensive apoptosis in the prostate tumor, and hence to a regression of the disease. However, . . . apoptosis is not complete, and a progression of surviving tumor cells to androgen-independence ultimately occurs." Id., page 1. The present invention is concerned with delaying the ultimate progression of tumor cells to androgen-independence.

Appellants "initially characterized the changes [in] IGFBPs expression in the Shionogi tumor model[1] after castration and during [progression to androgen-independence]" (Specification, page 5). "Of the IGBFPs expressed in Shionogi tumors, the most dramatic changes in expression were observed with IGFBP-5. Despite undetectable levels in [androgen-dependent] intact tumors, IGFBP-5 expression is highly upregulated after castration, and remains highly expressed in [androgen-independent] tumors." Id., pages 5-6. Moreover, "[t]he pattern of

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[1] "The Shionogi tumor model is a xenograft of an androgen-dependent mouse mammary carcinoma that grows subcutaneously in male syngenic hosts." Specification, pages 4-5. Shionogi tumor cells "are highly tumorigenic and locally invasive . . . [and] have been shown to respond to androgen withdrawal in a manner which mimics the observed behavior of prostatic tumor cells," that is, "androgen withdrawal precipitates apoptosis and tumor regression in a highly reproducible manner" (id., page 5). "Further, changes in expression of peptides . . . in human prostate cancer following castration and during progression to androgen-independence are similar to those observed in Shionogi tumor cells. Because of these similarities, the Shionogi tumor model mimics human prostate cancer and provides a very useful model for the evaluation of the ability of compounds to delay the onset of androgen-independence. Despite complete tumor regression after castration, rapidly growing androgen-independent Shionogi tumors invariably recur after one month, which provides a reliable end point to evaluate agents which can delay the progression to androgen-independence." Id.

IGFBP-5 upregulation in the Shionogi tumor model during [progression to androgen-independence] . . . is similar to that in rat prostate . . . and human prostate" (id., page 6).

According to appellants, antisense oligodeoxynucleotides (ODNs) complementary to portions of the gene encoding IGFBP-5 "inhibit[ ] cell proliferation and induce[ ] cell cycle arrest in Shionogi tumor cells in a time- and dose-dependent manner . . . [and do] not appear to induce apoptosis either in vitro or in vivo, . . . suggest[ing] that antisense IGFBP-5 activity occurs via inhibition of cell proliferation rather than induction of apoptosis." Id. Appellants "hypothesized that targeting upregulation precipitated by androgen using [an] antisense strategy might inhibit progression to androgen-independence." Id., page 7. In appellants' "in vivo experiments, administration of antisense IGFBP-5 after castration delayed time to [androgen-independence] . . . and inhibited [androgen-independent] recurrent tumor growth." Id.

THE CLAIMS

The present invention is directed to "a method for delaying the progression of hormone-regulated (prostatic or breast) tumor cells to hormone (e.g. androgen or estrogen) independence, a therapeutic method for the treatment of individuals . . . suffering from hormone regulated cancers, such as breast or prostate cancer, and therapeutic agents effective for use in such methods." Specification, page 4. In addition, the present invention is directed to a method of inhibiting or delaying metastatic boney progression of an IGF-1 sensitive tumor in a mammal. We note that the claims on appeal require an antisense oligonucleotide that inhibits expression of

IGFBP-5, with the exception of method claims 8, 12, 15, 19, 39 and 40, which merely require "a composition effective to inhibit expression of IGFBP-5."

Claims 1, 8, 15 and 22 are representative of the subject matter on appeal:

1. A method for delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state, comprising treating hormone-sensitive mammalian tumor cells with an antisense oligonucleotide which inhibits expression of IGFBP-5 by the tumor cells.

8. A method for treating a hormone-responsive cancer in a mammalian individual suffering from hormone-responsive cancer, comprising the steps of initiating hormone-withdrawal to induce apoptotic cell death of hormone-responsive cancer cells in the individual, and administering to the individual a composition effective to inhibit expression of IGFBP-5 by the hormone-responsive cancer cells, thereby delaying the progression of hormone-responsive cancer cells to a hormone-independent state in the individual.

15. A method for inhibiting or delaying metastatic boney progression of an IGF-1 sensitive tumor in a mammal, comprising the step of administering to the mammal a composition effective to inhibit expression of IGFBP-5 by the hormone-responsive cancer cells, thereby inhibiting or delaying metastatic boney progression of the tumor.

22. A composition for treatment of hormone-regulated cancer comprising an antisense oligonucleotide which inhibits expression of IGFBP-5 by hormone-regulated tumor cells.

THE REJECTIONS

The claims stand rejected as follows:

I. Claims 1, 5, 22 and 36-38[2] under 35 U.S.C. § 102 (b) as anticipated by Huynh.[3]

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[2] Claims 36-38 were subject to this ground of rejection in the final rejection (paper no. 14, January 24, 2003), but were omitted from the examiner's statement of the rejection in the Answer. The omission of these claims appears to have been a typographical error, as they are specifically discussed in the examiner's response to appellants' arguments (see, e.g., page 16 of the Answer).

[3] Huynh et al., "A Role for Insulin-like Growth Factor Binding Protein 5 in the Antiproliferative Action of the Antiestrogen ICI 182780," Cell Growth & Differentiation, Vol. 7, pp. 1501-1506 (November 1996)

II. Claims 1-3, 5, 6, 22, 23, 26-28, and 36-38[4] under 35 U.S.C. § 103 (a) as unpatentable over Huynh in view of Kiefer,[5] Baracchini[6] and Nickerson.[7]

III. Claims 1-3, 4, 6, 8-10, 12, 13, 15-17, 19, 20, 22, 23 and 38-40 under the first paragraph of 35 U.S.C. § 112, written description.

IV. Claims 1-23 and 26-40 under the first paragraph of 35 U.S.C. § 112, enablement.

DISCUSSION

I. Anticipation

Claims 1, 5, 22 and 36-38 stand rejected under 35 U.S.C. § 102 (b) as anticipated by Huynh. Claims 1, 5 and 38 are method claims, while claims 22, 36 and 37 are composition claims. Appellants argue that the method and composition claims do not stand or fall together because "anticipation of a method claim requires a different content of the reference than a composition claim, which need only disclose the same composition, rather than the same method steps." Brief, page 3. Accordingly, we will consider claim 1 to be representative of the method claims, and claim 22 to be representative of the composition claims – claims 5 and 38 will stand or fall with claim 1, while claims 36 and 37 will stand or fall with claim 22.

Claim 1 is directed to a method of delaying progression of hormone-regulated

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[4] Claim 40 was included in this rejection in the final rejection, but the rejection was withdrawn with respect to claim 40 in the Examiner's Answer (page 17).

[5] Kiefer et al., "Molecular Cloning of a New Human Insulin-like Growth Factor Binding Protein," Biochem. Biophys. Res. Commun., Vol. 176, No. 1, pp. 219-225 (1991).

[6] U.S. Patent No. 5,801,154, issued to Baracchini et al. on September 1, 1998.

[7] Nickerson et al., "Castration-Induced Apoptosis in the Rat Ventral Prostate is Associated with Increased Expression of Genes Encoding Insulin-Like Growth Factor Binding Proteins 2, 3, 4 and 5," Endocrinology, Vol. 139, No. 2, pp. 807-810 (1998).

mammalian tumor cells to an androgen-independent state by treating the cells with an antisense oligonucleotide which inhibits expression of IGFBP-5 by the tumor cells. According to the examiner, "a key limitation is that the method steps are carried out in hormone sensitive mammalian tumor cells" (Answer, page 14), and "Huynh discloses administering an antisense oligomer comprising 21 nucleotides targeted to IGFBP-5 to breast cancer cells" (id., page 5). The examiner acknowledges that Huynh says nothing about delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state, but argues that "any recited outcome such as that is merely considered to be an inherent feature, since all the structural and manipulative features of the claim are present in Huynh" (id.).

It is well settled that a prior art reference may anticipate even when claim limitations are not expressly found in that reference, but are nonetheless inherent in it. See, e.g., Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999); Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). However, it is also the case that "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Here, Huynh teaches that "IGFBP-5 can either stimulate or inhibit cellular proliferation in different experimental systems . . . suggest[ing] that there are poorly characterized complexities in IGFBP-5 action" (Huynh, pages 1503-1504). Indeed, on this record, there is no dispute that "Huynh [ ] actually teach[es] that antisense to IGFBP-5 stimulates cell proliferation in the [MCF-7] breast cancer cell line used" (Answer, page 14), while it inhibits proliferation in the Shionogi tumor cells used by

appellants. According to the examiner, this variation in the effects of antisense IGFBP-5 is irrelevant "because cellular proliferation (or inhibition thereof) is not recited as a claim limitation" (id.). In our view, however, this variation is relevant because it shows that in the only directly comparable parameter of record, the two cell lines react differently to inhibition of IGFBP-5. While Huynh says nothing about delayed progression to androgen-independence, it is not unreasonable to expect that the two cell lines might react differently to inhibition of IGFBP-5 in this respect as well, especially in light of Huynh's suggestion that the actions of IGFBP-5 are poorly characterized. In our view, the examiner has established that inhibition of IGFBP-5 in Huynh's MCF-7 cells might delay progression to androgen-independence, but has not established that it will. As discussed above, this is not sufficient to establish a prima facie case of anticipation based on inherency.

Accordingly, the rejection of claims 1, 5 and 38 as anticipated by Huynh is reversed.

Claim 22, however, stands on a different footing. Claim 22 is directed to "a composition for treatment of hormone-regulated cancer comprising an antisense oligonucleotide which inhibits expression of IGFBP-5 by hormone-regulated tumor cells." Huynh plainly describes an IGFBP-5 antisense oligodeoxynucleotide which reduces expression of IGFBP-5 in human breast cancer cells. Appellants argue that "the phrase 'for treatment of hormone-regulated cancer' is more than a statement of intended use and deserves to be given weight in assessing the scope of the claims." Brief, page 7. According to appellants, "Huhnh's antisense is not used in the treatment of any animal or human . . . [thus,] [t]here is no teaching of a composition suitable for

administration in the treatment of cancer." Id. Nevertheless, appellants have not pointed out anything which makes Huynh's IGFBP-5 antisense oligonucleotide composition unsuitable for administration to an animal, or which distinguishes it from the claimed IGFBP-5 antisense oligonucleotide composition in any way.

Accordingly, the rejection of claim 1 as anticipated by Huynh is affirmed. As discussed above, claims 36 and 37 stand or fall with claim 22, thus the rejection of claims 36 and 36 as anticipated by Huynh is affirmed as well.

II. Obviousness

Claims 1-3, 5, 6, 22, 23, 26-28, and 36-38 stand rejected under 35 U.S.C. § 103 (a) as unpatentable over Huynh in view of Kiefer, Baracchini and Nickerson. Having already determined that Huynh anticipates the subject matter of claims 22, 36 and 37, we affirm the rejection under 35 U.S.C. § 103 (a) with respect to those claims. "[A]nticipation is the epitome of obviousness." Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983).

Claims 1-3, 5, 6, 23, 26-28 and 38, on the other hand, are directed to methods of delaying the progression of hormone-regulated tumor cells to an androgen-independent state; to treating a hormone-responsive cancer; and to delaying metastatic boney progression of IGF-1 sensitive tumors by inhibiting IGFBP-5.

The examiner relies on Huynh for disclosure of "an antisense oligomer comprising 21 nucleotides targeted to IGFBP-5 that was administered to breast cancer cells" (Answer, page 6); on Kiefer for disclosure of the translation initiation and termination regions of IGFBP-5 (id.); and on Baracchini for "teach[ing] that the translation initiation and termination regions are preferred regions for targeting with

antisense oligos" (id.). According to the examiner, these references provide motivation for targeting particular regions of IGFBP-5 in order to inhibit its effects. Id., pages 6-7.

Nevertheless, in our view, the dispositive issue here is the examiner's proposed rationale for inhibiting IGFBP-5 in tumor cells in the first place. The underlying premise of the examiner's rejection is that "Nickerson teaches that prostatic tumor cells over-express IGFBP-5 and [that IGFBP-5] is involved in tumorigenesis" (id., page 6), and that, therefore, it would have been obvious for one skilled in the art to inhibit IGFBP-5 expression in prostatic tumor cells (id., page 7).

We see no factual basis for the examiner's expansive interpretation of Nickerson's teachings. Nickerson's experiments were designed "to study the gene expression of IGFBPs during involution of the rat ventral prostate after castration." Nickerson, page 807. The experiments demonstrated that "IGFBP-5 mRNA increases in the ventral prostate 2-fold by 24 h and 5-fold by 72 h [ ] in keeping with the hypothesis that IGFBP-5 may be involved in apoptosis resulting from steroid hormone deprivation." Id., page 809, left-hand column. According to Nickerson, the experimental system could not determine "whether IGFBPs cause apoptosis in the ventral prostate or are upregulated as a result of apoptosis." Id., right-hand column. Either way, the examiner has not explained how Nickerson's observations suggest that IGFBP-5 is involved in tumorigenesis, or why one skilled in the art would have wanted to inhibit its effects.

The examiner bears the initial burden of establishing prima facie obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a prima facie conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See In re Lowry, 32 F.3d 1579, 1582, 32

USPQ2d 1031, 1034 (Fed. Cir. 1994). In addition, the record must provide evidence that those of skill in the art would have had a reasonable expectation of success in doing so. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

We agree with appellants that the examiner's rejection "fails to state a prima facie case of obviousness." Brief, page 8. The rejection of claims 1-3, 5, 6, 23, 26-28 and 38 under 35 U.S.C. § 103 is reversed.

III. Written Description

Claims 1-3, 4, 6, 8-10, 12, 13, 15-17, 19, 20, 22, 23 and 38-40 stand rejected under the first paragraph of 35 U.S.C. § 112, as lacking adequate written descriptive support.

"The 'written description' requirement serves a teaching function, . . . in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 922, 69 USPQ2d 1886, 1891 (Fed. Cir. 2004) (citation omitted). Another "purpose of the 'written description' requirement is . . . [to] convey with reasonable clarity to those skilled in the art that, as of the filing date [ ], [the applicant] was in possession of the invention." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). See also Enzo Biochem Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1329, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). The requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." University of Rochester, 358 F.3d at 928, 69

USPQ2d at 1896. Whether or not a specification satisfies the requirement is a question of fact, which must be resolved on a case-by-case basis (Vas-Cath, 935 F.2d at 1562-63, 19 USPQ2d at 1116), and it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)).

With respect to claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38, we disagree with the examiner's rationale and conclusion. These claims require antisense oligonucleotides, of varying scope, which inhibit expression of IGFBP-5 in hormone-regulated mammalian tumor cells. The examiner argues that "[t]he specification . . . only describes two target IGFBP-5 sequences, [mouse and human] . . . , and does not describe any additional sequences that can be targeted via antisense oligos. Without such a description, the skilled artisan would not be able to envision any other target sequences and thus would not be able to synthesize an antisense oligo specific for the sequence" (Answer, page 8), and moreover, would be "required to undertake de novo experimentation to isolate and identify IGFBP-5 encoding nucleic acids" (id.).

Nevertheless, "applicants have some flexibility in the 'mode selected for compliance' with the written description requirement" (University of Rochester, 358 F.3d at 928, 69 USPQ2d at 1896), and it is well settled that actual reduction to practice is not necessary to satisfy the requirement (id. at 926, 69 USPQ2d at 1894). On the other hand, "[i]n claims to genetic material . . . [a] definition by function . . . does not suffice to to define [a] genus because it is only an indication of what the [material] does, rather than what it is." University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court explained that "[a]n adequate written

description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,'" (id. at 1566, 43 USPQ2d at 1404) while "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus" (id. at 1568, 43 USPQ2d at 1406). Subsequently, the court clarified that "the written description requirement would be met for [a claim] . . . if [a] functional characteristic . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Enzo Biochem, 296 F.3d at 1324-25, 63 USPQ2d at 1613.

Here, the specification sets forth the sequences of DNA molecules encoding the mouse and human IGFBP-5s, as well as a number of antisense sequences targeting specific regions of the mouse and human IGFBP-5 DNAs. The examiner's rationale would seem to limit the claimed genus to only those antisense oligonucleotides explicitly recited, without explaining why one skilled in the art would not have expected the mouse and human DNAs to be representative of, or have considerable structural similarity to, DNA encoding IGFBP-5 in other mammals. Again, it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (Wertheim, 541 F.2d at 263, 191 USPQ at 97). We find that the examiner has not done so.

Accordingly, the rejection of claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38 as lacking adequate written descriptive support under 35 U.S.C. § 112, first paragraph, is reversed.

With respect to claims 8, 12, 15, 19, 39 and 40, however, we agree with the examiner that adequate written descriptive support is lacking. We note that these claims merely require "a composition" effective to inhibit expression of IGFBP-5. The only such compositions disclosed in the specification are the afore mentioned antisense oligonucleotides. The examiner's position is essentially that the specification does not provide "any description, structural[ ] or otherwise, of IGFBP-5 inhibitors other than the instantly described antisense oligo[nucleotides]" and that the instantly described antisense oligonucleotides are "not representative of the breadth of inhibitors sought in the instant claims" (Answer, page 8).

Appellants argue that "the invention is based on the discovery . . . that reducing the expression of IGFBP-5 in hormone-responsive cancer cells has therapeutic benefits" (Brief, page 12), and "antisense inhibitors of IGFBP-5 expression [are] examples of a methodology that can be used in practicing the methods" (id., page 13). Appellants argue that the invention "is not antisense technology per se. It is also not the identification of IGFBP-5, nor any and all inhibitors of IGFBP-5 expression" (id., page 12).

These arguments are not persuasive. The Federal Circuit has recently held that the written description standard discussed in Eli Lilly applies to methods as well as products. See University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 926, 69 USPQ2d 1886, 1894 (Fed. Cir. 2004): "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods."

The facts in Rochester are similar to those of the instant application. Rochester involved a "method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment." Id. at 920, 69 USPQ2d at 1888 (emphasis added). The court noted that the relevant patent described the cells needed to screen for compounds having the recited property, as well as "assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product." Id. At 927, 69 USPQ2d at 1895. Nevertheless, the court concluded that the patent's disclosure was inadequate to enable the claimed method because the patent "[did] not disclose just which peptides, polynucleotides, and small organic molecules have the desired characteristic of selectively inhibiting PGHS-2." Id. (emphasis in original, internal quotations omitted). "Without such disclosure, the claimed methods cannot be said to have been described." Id.

In this case, as in Rochester, the claims are directed to a process for accomplishing a desired result (in Rochester, selectively inhibiting PGHS-2 activity in a human host; here, "inhibiting expression of IGFBP-5 in hormone-responsive cells") using a composition having a specified functional property (in Rochester, a "non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product"; here, "a composition effective to inhibit expression of IGFBP-5"). And in this case, as in Rochester, the specification provides no description whatsoever of just which compositions have the functional property recited in the claims - the genus recited in the claims is defined exclusively in functional terms, i.e., in terms of what the members of the genus do, rather than what they are.

As discussed above, "[a] definition by function . . . does not suffice to define [a] genus because it is only an indication of what the [material] does, rather than what it is." Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. To paraphrase Eli Lilly, naming a type of material, which may or may not exist, in the absence of knowledge as to what that material consists of, is not a description of that material. See id. Accordingly, the rejection of claims 8, 12, 15, 19, 39 and 40 as lacking adequate written descriptive support under 35 U.S.C. § 112, first paragraph, is affirmed.

IV. Enablement

Claims 1-23 and 26-40, all the claims on appeal, stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. According to the examiner, the claims are drawn to "antisense oligo[nucleotides] targeted to any transcript of IGFBP-5 as well as methods of treatment using said antisense oligo[nucleotides]" (Answer, page 9), but the specification "is only enabling for antisense oligos of SEQ ID NO:1 targeted to the IGFBP-5 transcripts of [murine] SEQ ID NO:13, and for the use of SEQ ID NOS; 2, 3 and 9 in the inhibition of SEQ ID NO:14 in vitro, and does not provide guidance on the in vivo inhibition of [human] SEQ ID NO:14" (id.).

With respect to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48, all of which require an antisense oligonucleotide capable of inhibiting expression of IGFBP-5, we do not agree with the examiner's rationale or conclusion, for the reasons that follow. Initially, however, we note that the examiner has focused exclusively on the therapeutic use of antisense oligonucleotides, and has not separately addressed the enablement of those claims that do not require antisense oligonucleotides (as was done in the written description rejection above). Nevertheless, our affirmance of the written description rejection for claims 8, 12, 15, 19, 39 and 40 constitutes a disposition of these broader

claims, so we need not reach the merits of the enablement rejection with respect to these claims.

Returning to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48, then, we find that the reasons cited in support of the examiner's rejection are insufficient to support the examiner's conclusion that these claims are not enabled by the specification.

"The first paragraph of 35 U.S.C. § 112 requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).[8] That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). Nevertheless, "[w]hen rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes,

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> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).
>
> In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

According to the examiner, "the clinical application of antisense therapy is a highly unpredictable art due to obstacles that still face antisense therapy" (Answer, page 9). The obstacles enumerated by the examiner are essentially: the identification of an appropriate target in the disease process; the identification of a molecule that can interfere with the disease process through specific recognition and affinity; the complexity of cellular uptake of oligonucleotides; and physical barriers due to internal structures of target RNAs and associations with cellular proteins. Id., pages 9-10. In addition, the examiner relies on Gewirtz[9] and Branch[10] as evidence that "'the antisense approach has generated controversy [among those of skill in the art] with regard to mechanism of action, reliability, and ultimate therapeutic utility'" (id., page 10), and the sense in the art is that "'efforts should be increased . . . to learn how they may be used successfully in the clinic'" (id.).

We have no reason to doubt the examiner's assessment of the state of the art in general, and we think it is fair to say that the field of antisense therapy is indeed recognized as highly unpredictable by those of skill in the art. Nevertheless, appellants point out, and the examiner appears to acknowledge, that appellants have identified the murine and human IGFBP-5s as appropriate targets in treating androgen-dependent cancers like prostate cancer and breast cancer, and that appellants have identified

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[9] Giwirtz et al., "Facilitating Oligonucleotide Delivery: Helping Antisense Deliver on Its Promise," Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 3161-3163 (April, 1996).

[10] Branch, A.D., "A Good Antisense Molecule is Hard to Find," TIBS, Vol. 23, pp. 50 (February, 1998).

antisense IGFBP-5 molecules that can delay progression to androgen independence in the Shionogi tumor model (asserted to be a useful model of human prostate cancer) and/or inhibit expression of IGFBP-5 in human prostate cancer cell lines. See page 17 of the substitute Brief for Appellant (submitted June 10, 2004), and page 9 of the Answer. This concrete guidance, in the form of working examples, would seem to address a number of the examiner's specific concerns, and weigh in favor of finding the specification enabling for claims directed to antisense inhibition of IGFBP-5. In any case, the examiner has not explained why the specific guidance in the specification would not, at least to some extent, mitigate or counterbalance any remaining factors (e.g., the generally unpredictable nature of the field) tending to weigh against a finding of enablement. In other words, the examiner has not explained why identifying other antisense IGFBP-5 molecules capable of delaying progression of hormone-regulated tumor cells to androgen-independence, either in vivo or in vitro would have required undue experimentation, given the specific guidance provided by appellants in their working examples.

Accordingly, the rejection of claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48 as lacking enablement under the first paragraph of 35 U.S.C. § 112 is reversed.

SUMMARY

I. The rejection of the claims under 35 U.S.C. § 102 (b) as anticipated by Huynh is affirmed with respect to claims 22, 36 and 37, and reversed with respect to claims 1, 5 and 38.

II. The rejection of the claims under 35 U.S.C. § 103 (a) as unpatentable over Huynh, Kiefer, Baracchini and Nickerson is affirmed with respect to claims 22, 36 and 37, and reversed with respect to claims 1-3, 5, 6, 23, 26-28 and 38.

III. The rejection of the claims under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support is affirmed with respect to claims 8, 12, 15, 19, 39 and 40, and reversed with respect to claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38.

IV. The rejection of the claims under 35 U.S.C. § 112, first paragraph, as lacking enablement is reversed with respect to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48. We do not reach the merits of this rejection with respect to claims 8, 12, 15, 19, 39 and 40.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136 (a).

AFFIRMED-IN-PART

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

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